



Online ISSN (2789-3219)

Research Article

Effectiveness of Intralesional Vitamin D and Bleomycin Injections in Treating Recalcitrant Plantar Wart: A Comparative Study

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Received: 29 May 2025; Revised: 5 July 2025; Accepted: 8 July 2025

Abstract

Background: Intralesional injections of vitamin D and bleomycin have gained growing clinical interest in the treatment of recalcitrant plantar warts, with pain as a major limitation associated with their use. **Objective:** To assess the clinical outcomes of vitamin D and bleomycin in managing treatment-resistant plantar warts. **Methods:** An interventional comparative study conducted on patients diagnosed with recalcitrant plantar warts over 9 months and not treated for two months. Patients were divided randomly into two groups: group A (24 patients received intralesional vitamin D) and group B (24 patients received intralesional bleomycin). The clearance rate and pain score were estimated by visual analogue scale (VAS). **Results:** 48 patients were enrolled in the study. Bleomycin produced significantly greater reduction in wart size at early time points (2, 4, 6, and 8 weeks). Vitamin D also resulted in wart size reduction but with less consistency. By the 4-month follow-up, both treatment groups showed substantial clearance, with no statistically significant difference in overall outcomes. Vitamin D produced significantly lower pain scores at 1, 2, and 3 weeks, indicating better tolerability. By week 8, VAS scores between the groups converged and were no longer significantly different. **Conclusions:** Intralesional bleomycin and vitamin D are effective in the treatment of recalcitrant plantar warts. Bleomycin produced more rapid lesion regression, whereas vitamin D exhibited a more favorable tolerability profile.

Keywords: Adult, Adverse effects, Bleomycin, Intralesional injection, Vitamin D, Warts.

فعالية حقن فيتامين د و بليومايسين داخل الآفة في علاج الثآليل الأخمصية المتعددة: دراسة مقارنة

الخلاصة

الخلفية: اكتسبت الحقن داخل الآفة من فيتامين د والبليومايسين اهتماماً سريرياً متزايداً بعلاج الثآليل الأخمصية المقاومة للعلاج، مع وجود الألم كعقبة رئيسية مرتبطة باستخدامها. **الهدف:** تقييم النتائج السريرية لفيتامين د والبليومايسين في علاج الثآليل الأخمصية المقاومة للعلاج. **أساليب:** أجريت دراسة مقارنة تدخلية على المرضى الذين تم تشخيصهم بالثآليل الأخمصية المقاومة على مدى 9 أشهر ولم يعالجوا لمدة شهرين. تم تقسيم المرضى بشكل عشوائي إلى مجموعتين: المجموعة أ (تلقي 24 مريضاً فيتامين د داخل الآفة) والمجموعة ب (تلقي 24 مريضاً بليومايسين داخل الآفة). تم تقدير معدل الشفاء ودرجة الألم بواسطة المقياس التناظري البصري (VAS). **النتائج:** تم تسجيل 48 مريضاً في الدراسة. أنتج البليومايسين انخفاضاً أكبر بكثير في حجم الثآليل في النقاط الزمنية المبكرة (2 و 4 و 6 و 8 أسابيع). أدى فيتامين د أيضاً إلى تقليل حجم الثآليل ولكن بوقوع أقل. وبحلولو المتابعة التي استمرت 4 أشهر، أظهرت كلتا المجموعتين العلاجيتين نجاحاً كبيراً، مع عدم وجود فرق يعنّد به إحصائياً في النتائج الإجمالية. أنتج فيتامين د درجات ألم أقل بشكل ملحوظ في 1 و 2 و 3 أسابيع، مما يشير إلى قدرة تحمل أفضل. بحلول الأسبوع 8، تقاربت درجات VAS بين المجموعتين ولم تعد مختلفة بشكل كبير. **الاستنتاجات:** البليومايسين داخل الآفة وفيتامين د فعالان في علاج الثآليل الأخمصية المتعددة. أنتج البليومايسين انحسار الآفة أسرع، بينما أظهر فيتامين د درجة تحمل أكثر ملاءمة.

* **Corresponding author:** Shaymaa K. Abdulqader, Department of Radiology, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq; Email: shaymaa.k@kmc.uobaghdad.edu.iq**Article citation:** Jasim SA, Helmi R, Abdulqader SK. Effectiveness of Intralesional Vitamin D and Bleomycin Injections in Treating Recalcitrant Plantar Wart: A Comparative Study. *Al-Rafidain J Med Sci.* 2025;9(1):105-109. doi: <https://doi.org/10.54133/ajms.v9i1.2124>© 2025 The Author(s). Published by Al-Rafidain University College. This is an open access journal issued under the CC BY-NC-SA 4.0 license (<https://creativecommons.org/licenses/by-nc-sa/4.0/>).

INTRODUCTION

Plantar warts (verrucae plantaris) are prevalent skin lesions that appear on the sole caused by the human papillomavirus (HPV). The virus is widespread in the environment, resulting in a high incidence of asymptomatic infection that is usually eliminated by cellular or humoral immune response [1]. While many cases resolve spontaneously, a significant proportion become recalcitrant, necessitating medical intervention. A recalcitrant plantar wart is defined as a plantar wart that persists for more than two years and fails to respond to at least two standard therapeutic modalities, which pose substantial therapeutic challenges in dermatological practices [2]. Recent advancements have

introduced novel therapeutic modalities aimed at enhancing treatment efficacy and patient outcomes [1,3]. Among the wide array of emerging therapies, intralesional agents such as vitamin D₃ and bleomycin have gained growing clinical interest for their immunomodulatory and cytotoxic mechanisms, respectively [4]. Although the use of bleomycin dates back to the 1970s, its use is hindered by significant pain associated with plantar injection, in addition to local side effects including ulceration and altered skin pigmentation, and when injected near nails, it carries a risk of subungual hemorrhage, Raynaud's phenomenon, and digital ischemia [5,6]. As a result, dermatologists continue to explore new therapeutic agents, including intralesional vitamin D₃ injections over the traditional bleomycin, in an

attempt to overcome the unwanted side effects and for a better safety profile [7,8]. Intralesional vitamin D is assumed to be much less painful, which significantly enhances patients' compliance and offers a compelling alternative, especially for patients where tolerability is a significant concern [9]. Despite their increasing use worldwide, comparative evidence evaluating the efficacy and safety of intralesional vitamin D₃ versus bleomycin in recalcitrant plantar warts in Iraq remains limited. This study aims to critically assess and compare the clinical outcomes of these two treatment modalities, providing evidence-based insights into their therapeutic potential in managing treatment-resistant plantar warts.

METHODS

Study design and setting

An interventional comparative study recruited patients diagnosed with recalcitrant plantar warts to compare the effectiveness of intralesional injection of vitamin D to bleomycin. The study was conducted in the Department of Dermatology and Venereology in Al-Kindy Teaching Hospital, Baghdad, Iraq, during a period of nine months from the 1st of June 2024 to the end of March 2025. Verbal informed consent was obtained from all patients prior to data collection. To assure anonymity, personal identifiers were removed and replaced by identification codes. Administrative approvals were granted from the Department of Dermatology and Venereology at Al-Kindy Teaching Hospital.

Inclusion criteria

Patients diagnosed with recalcitrant plantar warts for more than 2 years and free of treatment in the last two months were included in the study.

Exclusion criteria

The exclusion criteria include patients who had any of the following: 1) pregnant and lactating women, 2) history of Raynaud's disease or peripheral vascular disorder, 3) history of other chronic systemic illness and immunosuppression, 4) age < 15 and > 60 years, and 5) infection at site of lesion.

Intervention and data collection

Data collection was conducted using a structured questionnaire administered by the researcher through face-to-face interviews with all participants. The instrument was designed to obtain comprehensive demographic information and relevant medical history, including age, gender, and details regarding the number and size of warts. To compare the effectiveness of the two modalities of treatment, patients were divided randomly into two groups and assigned a number. The patients with odd numbers were assigned as group A (24 patients received intralesional vitamin D₃), and the patients with even numbers were assigned as group B (24 patients received intralesional bleomycin). Regarding group A, the patients were treated with intralesional vitamin D₃ injections of 300,000 IU of cholecalciferol ampule (7.5 mg/ml) (ABIOTEN pharma®) for a maximum of four sessions (two weeks apart). Each wart and adjacent skin were sterilized with povidone iodine, then an intralesional injection of 2% lidocaine solution was introduced; then after a few minutes, vitamin D₃ was slowly injected into the base of each wart by using a 27-gauge insulin syringe with a dose of 0.2 ml/cm² till complete blanching was achieved, with a maximum of 1.0 ml used in a single session. The session

might be repeated at two-week intervals for a maximum of four weeks or stopped when there is a complete resolution of warts. The patients were instructed to use oral analgesia (NSAIDs) for pain relief and were advised not to use any topical medications. Regarding group B, the patients were treated by intralesional bleomycin injection in one session, which is available in a vial containing 15 U (Celon Lab Company®). First, it was diluted with 5 ml distilled water to prepare a 3 U/ml stock solution, which can be stored for 60 days at 4°–6°C. The two parts of lidocaine 2% and one part of bleomycin stock solution were taken in a 27-gauge insulin syringe to obtain the final concentration of 1.0 mg/ml. The lesions were sterilized with povidone iodine, and an intralesional 2% lidocaine injection was given. Then, after a few minutes, bleomycin 1.0 mg/ml was injected into wart lesions until complete blanching was achieved, and the amount of injection depended on the size of the warts: warts up to 5 mm, 10 mm, and more than 10 mm received 0.1 ml, 0.2 ml, and 0.3 ml, respectively, with a maximum amount limited to 1 ml in a single session. The participants in both groups were advised to manage pain using oral nonsteroidal anti-inflammatory drugs (NSAIDs) and were instructed to avoid the application of any topical treatments. All patients were instructed to return immediately if they experienced any unusual pain and to attend scheduled follow-ups for 2 weeks for the paring of eschar and assessing the response according to the follow-up schedule.

Assessment and follow-up

All patients in both groups were evaluated clinically by measuring the size of the lesions in millimeters in each follow-up session, comparing with the baseline measurement. Clinical photographic records were taken at each session for pretreatment and post-treatment comparison. Follow-up was done at 2, 4, 6, and 8 weeks and then after four months to assess treatment response, recurrence of local or systemic side effects, scarring, and pigmentary change. Physician global assessment was done by using a visual analogue scale (VAS) score at each visit [10].

Statistical analysis

Statistical computations were conducted using SPSS software version 25.0 (IBM Corp., Chicago, IL, USA). The normality of numerical variables was assessed by the Shapiro-Wilk test. Variables exhibiting normal distribution were presented as mean and standard deviation and analyzed using Student *t*-test. In contrast, data with non-normal distribution were summarized as median and ranges. The data was analyzed using Mann-Whitney U test. Categorical data were expressed as number and percentage and compared with the chi-square test. A *p*-value less than 0.05 was considered indicative of statistical significance.

RESULTS

The mean age in the vitamin D group was 31.63 ± 12.77 years, compared with 35.83 ± 8.46 years in the bleomycin group, with no significant difference ($p = 0.185$). Gender distribution was similar between groups, with males comprising 58.33% of the vitamin D group and 54.17% of the bleomycin group ($p = 0.771$). Regarding the number and size of warts, 50% of patients in both groups presented with two warts, and the median wart size was comparable between groups with similar ranges, as shown in Table 1. Data regarding wart size were non-normally distributed, so they were expressed as median and range and analyzed with a non-parametric Mann-Whitney U test.

Table 1: Baseline clinical and demographic characteristics of the patients based on treatment type (n=24 in each group)

Variables	Vitamin D	Bleomycin	p-value
Age (year)	33.6±12.8	35.8±8.5	0.185
Gender			
Male	14(58.33)	13(54.17)	0.771
Female	10(41.67)	11(45.83)	
Number of warts			
1	3(12.5)	6(25)	0.449
2	12(50)	12(50)	
≥3	9(37.5)	6(25)	
Wart size (mm)	16.2	15.5	0.788

Values were expressed as frequency, percentage, and mean ± standard deviation (SD). Independent samples t-test, Chi-square test, and Mann-Whitney U test are used for analysis.

The median wart sizes and their ranges were recorded at 2, 4, 6, and 8 weeks, as well as at 4 months. At earlier time points, bleomycin showed a significantly greater reduction in wart size compared to vitamin D, with *p*-values indicating statistical significance at 2 weeks (*p* = 0.031), 4 weeks (*p* = 0.038), 6 weeks (*p* = 0.013), and 8 weeks (*p* = 0.010). Vitamin D also reduced wart sizes but less consistently than bleomycin. By 8 weeks and at the 4-month follow-up, most warts were either cleared or nearly cleared in both treatment groups, with no significant differences observed (Table 2).

Table 2: Efficacy of vitamin D and bleomycin in reduction of recalcitrant planter warts size at different time points (n=24 in each group)

Time points	Wart size in response to either treatment modality		p-value
	Vitamin D	Bleomycin	
Baseline	16.2 (5.0-50.0)	15.5 (5.0-50.0)	0.788
2 weeks	13.75 (2.5-15.0)	8.75 (2.0-17.5)	0.031
4 weeks	8.75 (0.0-15.0)	5.0 (0.0-15.0)	0.038
6 weeks	6.25 (0.0-10.5)	1.25 (0.0-10.0)	0.013
8 weeks	2.0 (0.0-9.0)	0.8 (0.0-5.0)	0.010
4 months	0 (0.0-2.0)	0 (0.0-1.0)	1.00

Values are expressed as median and range.

By comparing the clearance rates of planter warts treated with vitamin D and bleomycin injections at follow-up visits. During the 6 weeks, bleomycin showed significantly higher clearance rates for planter warts compared to vitamin D (50% vs. 12.5%, *p* = 0.005), and this trend continued at 8 weeks (75% vs. 37.5%, *p* = 0.009). By the 4-month mark, both treatments maintained high clearance rates (75%) with no statistically significant difference between treatment modalities (*p* = 1.0), as seen in Table 3 and Figure 1.

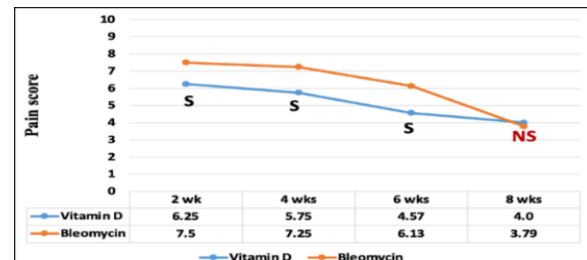
Table 3: Clearance rate for warts at different time points in vitamin D and bleomycin group (n= 24 in each group)

Time points	Treatment modality		p-value
	Vit. D	Bleomycin	
4 weeks			
Clear	3(12.5)	3(12.5)	1.00
Not clear	21(87.5)	21(87.5)	
6 weeks			
Clear	3(12.5)	12(50)	0.005
Not clear	21(87.5)	12(50)	
8 weeks			
Clear	9(37.5)	18(75)	0.009
Not clear	15(62.5)	6(25)	
4 months			
Clear	18(75)	18(75)	1.00
Not clear	6(25)	6(25)	

Values were expressed as frequency and percentage.

**Figure 1:** Clinical photographs illustrating the response of recalcitrant planter warts to intralesional treatment. A) Baseline image before bleomycin injection. B) Resolution of lesions 4 months after bleomycin treatment. C) Baseline image before vitamin D injection. D) Resolution of lesions 4 months after vitamin D treatment.

Figure 2 presents the mean Visual Analog Scale (VAS) scores—used to measure pain intensity—in patients treated with vitamin D and bleomycin for planter warts across four time points. At 1, 2, and 3 weeks, the vitamin D group consistently reported lower mean VAS scores (6.25, 5.75, and 4.57, respectively) compared to the bleomycin group (7.5, 7.25, and 6.13, respectively), with all differences being statistically significant (*p* < 0.001). However, by the 8th week, the scores converged (4.0 for vitamin D vs. 3.79 for bleomycin), and the difference was no longer statistically significant (*p* = 0.607).

**Figure 2:** Mean VAS score in vitamin D and bleomycin groups at different time points. S: significant at *p* < 0.05, NS: non-significant (*p* > 0.05).

DISCUSSION

The current study compared the efficacy and tolerability of intralesional vitamin D to bleomycin in treating recalcitrant planter warts. Bleomycin demonstrated a significantly greater reduction in wart size at early time points. Vitamin D also resulted in wart size reduction but with less consistency. Over 8 weeks and at the 4-month follow-up, both treatment groups showed substantial clearance, with no statistically significant difference in overall outcomes. In terms of pain assessment using the Visual Analogue Scale (VAS), the vitamin D group reported significantly lower scores at 1, 2, and 3 weeks, indicating better tolerability. By week 8, VAS scores between the groups converged and were no longer significantly different. Bleomycin, an antitumor antibiotic with cytotoxic properties, has been extensively used as an intralesional therapy for recalcitrant planter warts. It has a long-standing history in dermatological practice, and clinicians are experienced in its preparation, dosing, and administration protocols. While newer, less painful alternatives are being explored, bleomycin remains a cornerstone in the management of

recalcitrant plantar warts due to its high success rate and reliable performance [11,12]. Recently, intralesional vitamin D has gained increasing interest as a promising treatment modality to overcome the pain and cytotoxic effect associated with bleomycin, making it an appealing choice for dermatologists [13,14]. The current study demonstrates that intralesional vitamin D led to a more gradual and less consistent reduction in the size of recalcitrant plantar warts when compared to intralesional bleomycin. On follow-up to a 4-month visit, patients in both groups achieved a comparable clearance rate with no statistically significant difference ($p=1.00$), indicating that both achieved similar therapeutic effects in the treatment of recalcitrant plantar warts, but vitamin D took longer to exert its effect. This goes with previous results; a study by Prathibha *et al.* [15] reported no statistically significant difference in response between the two treatment modalities with no recurrence on follow-up after 3 months. Vitamin D showed a trend of higher efficacy in comparison with other treatment modalities in recalcitrant warts [5,16–18], this all advocates for potential use as a second- or even first-line agent in the treatment of recalcitrant plantar warts [13]. Pain represents significant consideration in the intralesional injection of plantar warts given the sensitive, densely innervated site, the weight-bearing nature, and the limited tissue compliance of the plantar surface [19]. In the current study, both treatment modalities caused pain when assessed by VVAS; the scores were significantly higher in bleomycin-treated patients early during treatment. However, at 2 months there were insignificant differences in pain perception between the two modalities of treatment. The high degree of pain linked with intralesional bleomycin was previously reported in the literature [6,11,12]. In a study by Aziz-Jalali [20], 86% of the patients treated with bleomycin reported pain at the injection site, especially during the first two days post-injection. The intense bleomycin-related pain is attributed to the cytotoxic effect on the surrounding tissue [21]. On the other hand, the pain associated with vitamin D is less in intensity and tolerable in most patients [14,15]. All this advocates for the use of intralesional vitamin D in patients where minimizing procedural pain is critical—such as in children, anxious patients, or those with multiple lesions. The choice between bleomycin and vitamin D for intralesional treatment of plantar warts should be guided not only by efficacy but also by patient-specific considerations, particularly pain tolerance and treatment setting.

Study limitations

This study is limited by a small sample size and single-center design that prevents generalizability of the results. However, the results add to the growing body of evidence supporting the use of intralesional vitamin D in the treatment of recalcitrant plantar warts.

Conclusion

Both intralesional bleomycin and vitamin D proved effective in treating recalcitrant plantar warts, with no significant difference in long-term clearance. While bleomycin showed a faster early response, vitamin D was better tolerated with significantly less pain. Both agents offer viable options, with selection guided by clinical context and patient preference.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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